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PATENT TRADEMARK OFFICE

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/03067	9 AUGUST 2000	12 AUGUST 1999

TITLE OF INVENTION
NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

APPLICANT(S)
PETER DAVID **DAVIS**

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE *The completion of those filing requirements that can be made at a time later than 30 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 USC 371(d) The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase See 37 C F R §1.491 which states "An international application enters the national state when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1 494 and § 1 495 "*

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**)*
(Express Mail certification is optional)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date February 6, 2002, in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EV 011020505 US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231

CONNIE YANNOTTI
(type or print name of person mailing paper)

Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C F R 1 8 cannot be used to obtain a date of mailing or transmission for this correspondence*

**WARNING:* *Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C F R 1 10(b)*
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition" Notice of Oct. 24, 1996, 60 Fed Reg 56,439, at 56,442

EXPRESS MAIL LABEL NO.: EV 011020505 US

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C F R §1 10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C F R §1 8*

NOTE. *Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C F.R. § 1.494(f).*

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS*	10 - 20 =		x $ 18.00 =	$
	INDEPENDENT CLAIMS*	3 - 3 =		x $ 84.00 =	
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $280.00				
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $100.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $710.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U S PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $740.00 [ ] has not been paid (37 CFR 1 492(a)(3)) ..... $1,040.00 [X] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $890.00				
				Total of above Calculations	890.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Statement may also be filed. (note 37 CFR 1.9, 1.27, 1.28)				-
				Subtotal	
				Total National Fee	$890.00
	Fee for recording the enclosed assignment document $40 00 (37 CFR 1 21(h)). (See Item 13 below) See attached "ASSIGNMENT COVER SHEET"				
TOTAL				Total Fees enclosed	$890.00

*May include Preliminary Amendment (see page 8) reducing the number of claims.

i. [X] A check in the amount of $890.00 to cover the above fees is enclosed.
ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

**WARNING. *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b)*

WARNING *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

[ ] Applicant hereby asserts status as a small entity under 37 C.F.R. § 1.27.
[ ] A Statement or Written Assertion is attached.

NOTE. *37 C.F.R. § 1.27(c) deals with the assertion of small entity status, whether by a written specific declaration thereof or by payment as a small entity of the basic filing fee or the fee for the entry into the national phase as states*

"(c) Assertion of small entity status. Any party (person, small business concern or nonprofit organization) should make a determination, pursuant to paragraph (f) of this section, of entitlement to be accorded small entity status based on the definitions set forth in paragraph (a) of this section, and must, in order to establish small entity status for the purpose of paying small entity fees, actually make an assertion of entitlement to small entity status, in the manner set forth in paragraph (c)(1) or (c)(3) of this section, in the application or patent in which such small entity fees are to be paid.

(1) Assertion by writing. Small entity status may be established by a written assertion of entitlement to small entity status. A written assertion must

(i) Be clearly identifiable,

(ii) Be signed (see paragraph (c)(2) of this section); and

(iii) Convey the concept of entitlement to small entity status, such as by stating that applicant is a small entity, or that small entity status is entitled to be asserted for the application or patent. While no specific words or wording are required to assert small entity status, the intent to assert small entity status must be clearly indicated in order to comply with the assertion requirement.

(2) Parties who can sign and file the written assertion. The written assertion can be signed by.

(i) One of the parties identified in §§ 1.33(b) (e.g., an attorney or agent registered with the Office), §§ 3.73(b) of this chapter notwithstanding, who can also file the written assertion;

(ii) At least one of the individuals identified as an inventor (even though a §§ 1.63 executed oath or declaration has not been submitted), notwithstanding §§ 1.33(b)(4), who can also file the written assertion pursuant to the exception under §§ 1.33(b) of this part; or

(iii) An assignee of an undivided part interest, notwithstanding §§ 1.33(b)(3) and 3.73(b) of this chapter, but the partial assignee cannot file the assertion without resort to a party identified under §§ 1.33(b) of this part

(3) Assertion by payment of the small entity basic filing or basic national fee The payment, by any party, of the exact amount of one of the small entity basic filing fees set forth in §§ 1 16(a), (f), (g), (h), or (k), or one of the small entity basic national fees set forth in §§ 1 492(a)(1), (a)(2), (a)(3), (a)(4) or (a)(5), will be treated as a written assertion of entitlement to small entity status even if the type of basic filing or basic national fee is inadvertently selected in error

(i) If the Office accords small entity status based on payment of a small entity basic filing or basic national fee under paragraph (c)(3) of this section that is not applicable to that application, any balance of the small entity fee that is applicable to that application will be due along with the appropriate surcharge set forth in §§ 1.16(e) or §§ 1 16(l)

(ii) The payment of any small entity fee other than those set forth in paragraph (c)(3) of this section (whether in the exact fee amount or not) will not be treated as a written assertion of entitlement to small entity status and will not be sufficient to establish small entity status in an application or a patent "

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE Section 1 495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office In accordance with PCT Rule 47 1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date " Notice of Jan 7, 1993, 1147 O.G. 29 to 40, at 35-36 See item 14c below

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
   i. [X] by the International Bureau.
   Date of mailing of the application (from form PCT/IB/308): _____.
   ii. [ ] by applicant on _____ (Date).

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [ ] is transmitted herewith.
b. [X] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____ (Date).
d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE. The Notice of January 7, 1993 points out that 37 C F.R. § 1 495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended The Notice further advises that "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1 121 In many cases, filing an amendment under section 1 121 is preferable since grammatical or idiomatic errors may be corrected " 1147 O G 29-40, at 36

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.
   ii. [ ] by applicant on _____ (Date).
c. [X] have not been transmitted as
   i. [X] applicant chose not to make amendments under PCT Article 19.
   Date of mailing of Search Report (from form PCT/ISA/210): APRIL 27, 2001.
   ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] will follow
c. [ ] is not required as the amendments were made in the English language.
d. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [ ] A copy of the international examination report (PCT/IPEA/409)
[ ] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [ ] Annex(es) to the international preliminary examination report
a. [ ] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [ ] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [ ] is not required as the annexes are in the English language.

JC10 Rec'd PCT/PTO 06 FEB 2002

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
    a. [ ] was previously submitted by applicant on _____. Date
    b. [ ] is submitted herewith, and such oath or declaration
        i. [ ] is attached to the application.
        ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
    c. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
    a. [X] is transmitted herewith.
    b. [ ] has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____.
    c. [ ] is not required, as the application was searched by the United States International Searching Authority.
    d. [ ] will be transmitted promptly upon request.
    e. [ ] has been submitted by applicant on _____. Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
    a. [ ] is transmitted herewith. Also transmitted herewith is/are:
        [ ] Form PTO-1449 (PTO/SB/08A and 08B).
        [ ] Copies of citations listed.
    b. [X] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
    c. [ ] was previously submitted by applicant on _____. Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

_____
_____
_____

14. [X] Additional documents:
    a. [ ] Copy of request (PCT/RO/101)
    b. [X] International Publication No. WO 01/12579
        i. [X] Specification, claims and drawing
        ii. [ ] Front page only
    c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
    d. [ ] Other

15. [X] The above checked items are being transmitted
    a. [ ] before 30 months from any claimed priority date.
    b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized*

NOTE: *"A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1 17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission Submission of the fee set forth in § 1 17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission " 37 C F R § 1 136(a)(3)*

NOTE: *"Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1 26(a).*

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425 .

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1 495(b)(2)) results in abandonment of the application, it would be best to always check the above box*

[ ] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: *Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only*

be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[X] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance 37 C.F.R § 1.311(b).

NOTE. 37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . prior to paying, or at the time of paying . . issue fee." From the wording of 37 C.F.R § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 25,858

WILLIAM R. EVANS
(type or print name of practitioner)

Tel. No.: (212)708-1930

LADAS & PARRY
P.O Address

Customer No.: 00140

26 WEST 61ST STREET
NEW YORK, NEW YORK 10023

Practitioner's Docket No. U 013864-1

PATENT

#4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: PETER D. DAVIS
INTERNATIONAL APPLICATION NO.: PCT/GB00/03067
INTERNATIONAL FILING DATE: AUGUST 9, 2000
SERIAL NO.: 10/049,248

For: NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the above identified application as follows:

IN THE CLAIMS :

Please amend claims 5, 9 and 10 as follows:

5. A prodrug of a cis-stilbene which is an carboxylic ester, phosphate ester, sulphate ester or carbonate of the cis-stilbene as claimed in claim 1.

9. A composition for use in the treatment of neovascularisation which composition contains an effective amount of the cis-stilbene according to claim 1.

CERTIFICATE UNDER 37 1.10

I hereby certify that this paper is being deposited with the United States Postal Service on this date APRIL 30, 2002 in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" Mailing Label Number EV011021925 US addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231

CONNIE YANNOTTI
(Type or print name of person mailing paper)

(Signature of person mailing paper)

NOTE: Each paper or fee referred to as enclosed herein has the number of the "EXPRESS MAIL" mailing label place thereon prior to mailing 37 CFR 1.16(b).

10. A method comprising preparing a composition for the treatment of neovascularisation with the cis-stilbene as claimed in claim 1.

Please add new Claims 11-14 as follows:

11. A prodrug of a cis-stilbene which is an carboxylic ester, phosphate ester, sulphate ester or carbonate of the cis-stilbene as claimed in claim 2.

12. A prodrug of a cis-stilbene which is an carboxylic ester, phosphate ester, sulphate ester or carbonate of the cis-stilbene as claimed in claim 3.

13. A composition for use in the treatment of neovascularisation which composition contains an effective amount of the prodrug according to claim 5.

14. A method comprising preparing a composition for the treatment of neovascularisation with the prodrug as claimed in claim 5.

15. A composition for use in the treatment of neovascularisation which composition contains an effective amount of the cis-stilbene according to claim 6.

16. A composition for use in the treatment of neovascularisation which composition contains an effective amount of the cis-stilbene according to claim 7.

17. A composition for use in the treatment of neovascularisation which composition contains an effective amount of the cis-stilbene according to claim 8.

Remarks

The above amendatory action is taken solely for the purpose of avoiding claim fees that would otherwise accrue due to the presence of multiple dependent claims.

Respectfully submitted,

JOHN RICHARDS
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG.NO.31,053 (212)708-1915

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5. A prodrug of a cis-stilbene which is an carboxylic ester, phosphate ester, sulphate ester or carbonate of [a] the cis-stilbene as claimed in [any one of] claim[s] 1 [to 3].

9. A composition for use in the treatment of neovascularisation which composition contains an effective amount of [a] the cis-stilbene according to [any one of] claim[s] 1 [to 4 or a prodrug thereof according to any one of claims 5 to 8].

10. [Use in the preparation of] A method comprising preparing a composition for the treatment of neovascularisation [of a] with the cis-stilbene as claimed in [any one of] claim[s] 1 [to 4 or a prodrug thereof according to any one of claims 5 to 8].

NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients, if this blood supply is mechanically shut off the tumour undergoes necrotic death Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.

Compounds able to damage neovasculature have advantages in the treatment of disease. For example, attacking tumour vasculature has several important advantages over a direct attack on the tumour. In particular the endothelial cells of tumour vasculature are more genetically stable than those of the tumour itself and are therefore less likely to become resistant to the damaging agent. Thus a major problem in conventional anti-tumour chemotherapy, that of drug resistance, is circumvented by this approach. Furthermore, since the endothelial cells of the tumour vasculature, unlike the tumour cells themselves, are similar between different solid tumour types, vascular damaging agents are able to attack a wide range of tumour types.

A number of tubulin-binding agents including the stilbenes combretastatin A1, combretastatin A4 (D J Chaplin *et al.*,British J. Cancer 27, S86-S88 (1996))and combretastatin A4 phosphate (D.J. Chaplin *et al.*, Anticancer Research 19, 189-196, (1999)) are known to selectively damage neovasculature of solid tumours in animal models. While there are reports of the activity of other analogues of combretastatin A4 in tubulin binding assays, in cytotoxicity assays and in tumour models there have been no reports of the vascular damaging activities of analogues. Since the activity of

tubulin-binding compounds against *in vitro* assays are poor predictors of selective vascular damaging activity and activity of such compounds *in vivo* can also be mediated by direct antimitotic effects on the tumour itself, no prediction can be made of the selective vascular damaging activity of known or novel analogues of the combretastatins from published reports. Thus compounds which have the advantages of a selective anti-vascular mechanism given above, rather than acting through a direct effect on the tumour tissue itself, are not apparent.

We have found a series of novel *cis*-stilbenes with vascular damaging activity. These compounds specifically damage newly-formed vascular endothelium, especially that associated with solid tumours, without affecting the normal, established vascular endothelium of the host species. Such compounds are of use in the prophylaxis and treatment of cancers involving solid tumours and in other diseases where there is inappropriate formation of new vasculature such as diabetic retinopathy, psoriasis, rheumatoid arthritis, macular degeneration and the formation of atherosclerotic plaques.

Known vascular-damaging stilbenes, combretastatin A1, combretastatin A4 and combretastatin A4 phosphate have a 4-methoxy group in the "B" ring. The compounds of the invention lack a 4-methoxy group in the ring corresponding to the "B" ring of combretastatin A4. Several studies suggest that substituting alternative groups for the 4-methoxy group in the B-ring of combretastatin A4 would considerably reduce biological activity:

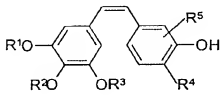
In J. Med. Chem 1991, 34, 2579-2588, Cushman *et al.* state, regarding analogues of combretastatin A4: "the presence of a 4-methoxy group in the B-ring plays a very important role for this compound to be highly cytotoxic" Replacement of the 4-methoxy group with chlorine, for example, gave compounds that were three to four orders of magnitude less potent against a panel of five different cell lines.

In J. Med. Chem. 1998, 41, 3022-3032 Ohsumi *et al.* disclose anilino analogues of combretastatin A4 in which the replacement of the B-ring 4-methoxy group by either a methyl group or a chlorine atom gave a reduction in biological potency of 8.5-fold and 13.5-fold respectively.

Similarly in Brit. J. Cancer 1995, 71, 705-711 Woods *et al.* disclose analogues of combretastatin with reduced potency. For example the 4-methyl compound shows 3.5 to 36-fold reduction in potency against four cell lines compared to the 4-methoxy compound.

It cannot be anticipated from the above studies that compounds in which the B-ring 4-methoxy group is replaced would retain anti-vascular activity It is particularly unexpected that replacing the B-ring methoxy group of combretastatin A4 would result in a compound with similar potency as a vascular damaging agent.

Thus according to one aspect of the invention we provide a compound of formula (1):



(1)

Wherein:

R^1,R^2 and R^3 are each independently alkyl,

R^4 is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo,

R^5 is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo,

and the pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

As used herein the term "alkyl", alone or in combinations, means a straight or branched-chain alkyl group containing from one to seven, preferably a maximum of four, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

An alkenyl group may be for example an olefinic group containing from two to seven carbon atoms for example methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene and t-butylene. An alkynyl group may be for example an ethynyl , propynyl or butynyl group.

Where one or more functional groups in compounds of formula (1) are sufficiently basic or acidic the formation of salts is possible. Suitable salts include pharmaceutically acceptable salts for example acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates, salts derived from inorganic bases including alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and salts derived from organic amines such as morpholine, piperidine or dimethylamine salts.

Prodrugs of the invention are compounds which upon administration to a mammal produce compounds of formula (1). Such prodrugs can be for example converted within the mammal by hydrolysis. Prodrugs are preferably ester derivatives of the phenolic hydroxy group contained in compounds of formula (1) such as, for example, phosphate esters, carboxylate esters, sulphate esters and carbonates.

Preferred compounds of the invention are those of formula 1 in which R^1, R^2 and R^3 are all methyl, and prodrugs thereof

Further preferred compounds of the invention are those of formula 1 in which R^1, R^2 and R^3 are all methyl and R^5 is hydrogen and prodrugs thereof

Still further preferred compounds of the invention are those of formula 1 in which R^1, R^2 and R^3 are all methyl, R^5 is hydrogen and R^4 is alkyl or halo and prodrugs thereof

Preferred prodrugs of the invention are phosphate esters. Particularly preferred prodrugs of the invention are dihydrogen phosphate esters.

Specifically preferred compounds of the invention are

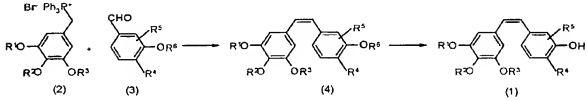
(*Z*)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

(*Z*)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate

Compounds of the invention can be prepared by any process known to a person skilled in the art. Compounds of formulae (1) can be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In the general preparations described below it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. In the following process description, the symbols R^1, R^2, R^3, R^4 and R^5, when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated

In one general example compounds of formula (1) can be prepared by Wittig olefin synthesis involving reaction of a phosphonium salt of formula (2) with a strong base, for example an alkyllithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether

or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 30°C followed by treatment with an aldehyde of formula (3) in which R^6 is a protecting group, to give an intermediate of formula (4) The synthesis of compounds of formula (1) is then completed by removal of the group R^6. Suitable protecting groups R^6 include trialkylsilyl, for example t-butyldimethylsilyl, and allyl. Where R^6 is a trialkylsilyl group it may be removed, for example, by treatment with a quaternary ammonium fluoride such as tetrabutylammonium fluoride in an ether solvent such as tetrahydrofuran at a temperature of about -30°C to about 40°C conveniently at or near ambient temperature Where R^6 is an allyl group it may be removed for example by treatment with a palladium(0) complex such as tetrakis(triphenylphosphine)Pd(0) in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of about -40°C to about 40°C conveniently at or near ambient temperature, in the presence of an allyl scavenger such as morpholine.

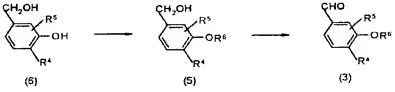


(2) (3) (4) (1)

Aldehydes of formula (3) can be prepared by any process known to a person skilled in the art. In one general example an aldehyde of formula (3) can be prepared from an alcohol of formula (5) by oxidation with a suitable oxidising agent Suitable oxidising agents include the Dess-Martin reagent and manganese dioxide Alcohols of formula (5) can be prepared by application of standard methods of organic synthesis including the selective protection of phenols of formula (6). Where the protecting group R^6 is a trialkylsilyl group, for example t-butyldimethylsilyl, alcohols of formula (5) may be prepared, for example, by treatment of a phenol of formula (6) with a strong base, for example an alkyllithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a

temperature of between about -100°C to about 40°C followed by treatment with *tert*-butylchlorodimethylsilane.

Phenols of formula (6) are either known or may be prepared from known compounds using standard methods of organic synthesis.



Compounds of formula (1) may also be prepared from other compounds of formula (1) by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, halogenation, oxidation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents.

Prodrugs of compounds of formula (1) can be prepared by any process known to a person skilled in the art Processes for the preparation of prodrugs of compounds of formula I include standard acylation, sulphation and phosphorylation reactions. In one general example dihydrogen phosphate esters of compounds of formula (1) can be prepared by treatment of the corresponding di-t-butylphosphate esters with an acid, for example hydrochloric acid or trifluoroacetic acid, in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of from about -20°C to about 40°C, conveniently at room temperature.

Compounds according to the invention are able to destroy tumour vasculature and vasculature that has been newly formed while leaving unaffected normal, mature vasculature. The ability of the compounds to act in this way may be determined by the tests described hereinafter

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

The compounds of the invention may be administered as a sole therapy or in combination with other treatments. Thus the invention includes compositions for the treatment of neovascularisation which compositions contain an effective amount of a cis-stilbene or prodrugs thereof as hereinbefore defined. The invention also includes the use in the preparation of a composition for the treatment of neovascularisation of a cis-stilbene or prodrugs therof as hereinbefore defined. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, vincristine, vinorelbine, paclitaxel and docetaxel; platinum derivatives for example cisplatin and carboplatin, alkylating agents, for example melphalan, chlorambucil, busulphan, ifosfamide and cyclophosphamide; antimetabolites, for example methotrexate, 5-fluorouracil, cytosine arabinoside, gemcitabine and hydroxyurea, antitumour antibiotics for example bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin,mitomycin-C, dactinomycin and mithramycin ; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide,teniposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab and trastuzumab, anti-hormones for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, anastrozole, letrazole, vorazole ,exemestane, flutamide, nilutamide and bicalutamide; anti-growth factor compounds for example EGFr tyrosine kinase inhibitors VEGFr kinase inhibitors and PDGFr tyrosine kinase inhibitors; and anti-angiogenesis agents such as angiostatin, endostatin and thalidomide. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution Topical administration may be as an ointment or cream and rectal administration may be as a suppository For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.1 to 10mg/kg.

BIOLOGICAL ACTIVITY

The following test was used to demonstrate the activity of compounds according to the invention.

Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). At least three animals were used in control and treated

groups. The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, **4**, 47-53, 1943) All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels. Examples of the activity of compounds of the invention in this test are given in the table.

Compound of Example	Dose (mg/kg)	% Reduction in Functional Vascular Volume
1	50	88
3	50	27
5	50	20

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

(Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

A solution of 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (491mg) in anhydrous tetrahydrofuran (10ml) at room temperature was treated slowly with a 1.1M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1ml) After 30 minutes crushed ice (5ml) and diethylether (30ml)

were added and the aqueous phase extracted with diethylether (5 portions of 5ml) The combined extracts were washed with water (3 portions of 10ml) and brine (10ml), dried (MgSO4) and concentrated under reduced pressure to give a solid. Recrystallisation from ethyl acetate/hexane gave the title compound (208mg) as a white solid m.p. 123-125°C. nmr: δH (500MHz, d6-DMSO) 2.07 (s, 3H), 3.57 (s, 6H), 3.62 (s, 3H), 6.40 (d, J = 12Hz, 1H), 6.46 (d, J = 12 Hz, 1H), 6.56 (s, 2H), 6.61 (dd, J = 8Hz, 2Hz, 1H), 6.76 (d, J= 1.7Hz, 1H), 6.98 (d, J = 8Hz, 1H), 9.21 (s 1H).

The 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene used as starting material in the above preparation was prepared as follows:
A suspension of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (848mg) in dry tetrahydrofuran (50ml) at -78°C was treated dropwise with n-butyllithium (0.9ml of a 1.8M solution in hexane) and the mixture allowed to warm to -40°C and stir for 1h. The mixture was recooled to -78°C and a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (390mg) in tetrahydrofuran (40ml) added slowly. After a further 2h the mixture was allowed to warm to room temperature before being poured into ice water (20ml). The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (3 portions of 20ml) and brine (2 portions of 20ml), dried (MgSO4) and concentrated under reduced pressure to give an oil. Purification by chromatography on silica gel, eluting with petroleum ether / ethyl acetate (90:10) gave 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (456mg) as a red oil.

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde used as starting material in the above preparation was prepared as follows:
A solution of Dess-Martin periodinane (187mg) in dichloromethane (4ml) was treated slowly with a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (100mg) in dichloromethane (4ml) and the mixture stirred for 1h at room temperature. Diethylether (10ml) was added followed by aqueous sodium thiosulphate solution (10ml) and the mixture stirred for 15 minutes. The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with aqueous

sodium thiosulphate solution (3 portions of 10ml), water (3 portions of 10ml) and brine (2 portions of 10ml), dried (MgSO4) and concentrated under reduced pressure to give a yellow solid. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (85mg).

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol used as starting material in the above preparation was prepared as follows:

A solution of 3-hydroxy-4-methylbenzyl alcohol (275mg) in dry tetrahydrofuran (15ml) at -78°C was treated slowly with n-butyllithium (1.2ml of a 1 8M solution in hexane) and the mixture stirred for 15minutes before being allowed to warm to room temperature and stir for a further 30minutes A solution of *tert*-butylchlorodimethylsilane (287mg) in tertrahydrofuran (10ml) was added and the mixture stirred for 16h. Water (20ml) was added and the mixture extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (2 portions of 10ml) and brine (20ml), dried (MgSO4) and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (390mg).

EXAMPLE 2

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate

Trifluoroacetic acid (0.22mL, 2.95mmol) was added dropwise to a stirred solution of (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate (401mg, 0 82mmol) and dichloromethane (16mL). The mixture was stirred at room temperature overnight. Solvent was removed *in vacuo*, and the residue azeotroped four times with toluene. The colourless oil was triturated with ether to give the title compound as a white solid (181mg, 58%) m.p 109-113°C nmr: δH (500MHz, d6-DMSO) 2.39 (s, 3H), 3.81 (s, 6H), 3.87 (s, 3H), 6.69 (d, J=12Hz, 1H), 6.74 (d,

J=12Hz, 1H), 6.78 (s, 2H), 7.07 (d, J=8Hz, 1H), 7.28 (d, J=8Hz, 1H), 7.49 (s, 1H), 9.0 (bs, 2H).

(*Z*)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate was prepared as follows:

Di-*tert*-butylphosphoramidite (498mg, 2.00mmol) in dichloromethane (1mL) was added to a solution of (*Z*)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (300mg, 1.00mmol), 1*H*-tetrazole (182mg, 2.60mmol) in dichloromethane (3mL) under nitrogen. After 2h, magnesium monoperoxyphthalate hexahydrate (1.24g, 2.00mmol) was added in portions. After stirring for a further 2h, the reaction mixture was partitioned between ethyl acetate and water; the aqueous phase was extracted (ethyl acetate x2), the combined organic extracts were washed (water x2, brine x1); dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography, eluting with 33% ethyl acetate/hexane, gave (*Z*)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate as a yellow oil (401mg, 82%).

EXAMPLE 3

(*Z*)-1-(4-fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

This compound was isolated directly from the Wittig reaction between 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-*tert*-butyldimethylsilyloxy-4-fluorobenzaldehyde (340mg) performed in an analogous manner to that of Example 1. There was obtained the title compound (80mg) as a colourless oil. nmr: (300MHz, d6-DMSO) 3.59 (s, 6H), 3.63 (s, 3H), 6.46 (d, J=12Hz, 1H), 6.48 (d, J=12Hz, 1H), 6.54 (s, 2H), 6.68 (m, 1H), 6.90 (dd, J=8.8, 2.1Hz, 1H), 7.06 (dd, J=11.4, 8.4Hz, 1H), 9.80 (s, 1H).

The following compounds were prepared in an analogous manner to that of Example 1:

EXAMPLE 4

(Z)-1-(4-chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

From (Z)-1-(3-*tert*-butyldimethylsilyloxy-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene (240mg) there was obtained the title compound (121mg) as a colourless oil. nmr: (300MHz, d6-DMSO) 3.59 (s, 6H), 3 63 (s, 3H), 6 49 (m, 2H), 6.54 (s, 2H), 6 71 (dd, J=8 2, 0 9Hz, 1H), 6.93 (d, J=0.9Hz, 1H), 7.25 (d, J=8.2Hz, 1H), 10.11 (bs, 1H).m/e 320 (M+).

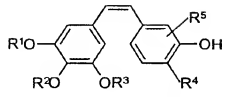
EXAMPLE 5

(Z)-1-(4-ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

From (Z)-1-(3-*tert*-butyldimethylsilyloxy-4-ethylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (926mg) there was obtained the title compound (208mg) as a white solid m.p. 105-107°C, nmr: δH (300MHz, CDCl3) 1.02 (t, J=7.6Hz, 3H), 2.6 (q, J=7.5Hz, 2H) 3.7 (s, 6H), 3.8 (s, 3H), 4.6 (bs, 1H), 6.4 (d, J = 12Hz, 1H), 6 5 (d, J = 12 Hz, 1H), 6.5 (s, 2H), 6.7 (s,1H), 6.8 (d, J= 7.6Hz, 1H), 7.0 (d, J = 7 6Hz, 1H).

CLAIMS:

1. A cis-stilbene of formula



(1)

Wherein:

R^1, R^2 and R^3 are each independently alkyl,
R^4 is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo,
R^5 is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo,
or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof.

2. A cis-stilbene according to claim 1 wherein
R^1, R^2 and R^3 are all methyl.

3. A cis-stilbene according to claim 2 wherein
R^5 is hydrogen and R^4 is alkyl or halo.

4. (*Z*)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene.

5. A prodrug of a cis-stilbene which is an carboxylic ester, phosphate ester, sulphate ester or carbonate of a cis-stilbene as claimed in any one of claims 1 to 3.

6. A prodrug of a cis-stilbene which is a phosphate ester of a cis-stilbene according to claim 1.

7. A prodrug according to claim 5 which is a dihydrogen phosphate ester.

8. (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate.

9. A composition for use in the treatment of neovascularisation which composition contains an effective amount of a cis-stilbene according to any one of claims 1 to 4 or a prodrug thereof according to any one of claims 5 to 8.

10. Use in the preparation of a composition for the treatment of neovascularisation of a cis-stilbene as claimed in any one of claims 1 to 4 or a prodrug thereof according to any one of claims 5 to 8.

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(71) Applicant *(for all designated States except US)*: ANGIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5S (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Watlington OX9 5SX (GB).

(74) Agents: BAILLIE, Iain, C. et al.; Langner Parry, 52-54 High Holborn, London WC1V 6RR (GB).

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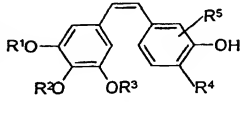
(54) Title: NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY



(1)

(57) Abstract: A group of novel cis-stilbenes as disclosed of formula (1) wherein: R^1, R^2 and R^3 are each independently alkyl, R^4 is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo, R^5 is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo, or a pharmaceutically acceptable salt thereof or a prodrug such as a phosphate ester. These compounds have vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularisation may have therapeutic benefit.

Practitioner's Docket No. U 013864-1 *PATENT*

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COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

[ ] original.
[ ] design.

NOTE With the exception of a supplemental oath or declaration submitted in a reissue, a supplemental oath or declaration is not treated as an amendment under 37 CFR 1.312 (Amendments after allowance). M.P.E.P. Section 714.16, 7th Ed.

[ ] supplemental.

NOTE. If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items.

[X] national stage of PCT.

NOTE. If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P

NOTE: See 37 C.F.R. Section 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.

[ ] divisional.
[ ] continuation.

NOTE Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C.F.R. Section 1.53(b) (application filing requirements-nonprovisional application).

[ ] continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: *If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.*

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) [ ] is attached hereto.

NOTE: "The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60).

(b) [ ] was filed on _____, [ ] as Application No. _____
[ ] and was amended on _____ (if applicable).

NOTE: Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 C.F.R. Section 1.67.

NOTE. "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63

(A) application number (consisting of the series code and the serial number, e.g., 08/123,456);
(B) serial number and filing date,
(C) attorney docket number which was on the specification as filed;
(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or
(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.

M.P.E.P. § 601.01(a), 7th ed.

(c) [X] was described and claimed in PCT International Application No. PCT/GB00/03067 filed on 9 August 2000 and as amended under PCT Article 19 on _____*(if any)*.

SUPPLEMENTAL DECLARATION (37 C.F.R. Section 1.67(b))

(complete the following where a supplemental declaration is being submitted)

[ ] I hereby declare that the subject matter of the

[ ] attached amendment
[ ] amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, Section 1.56,

(also check the following items, if desired)

[ ] and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

[ ] in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 C.F.R. Section 1.98.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

NOTE: 37 C.F.R. § 1.55 Claim for foreign priority.

"(a) An applicant in a nonprovisonal application may claim the benefit of the filing date of one or more prior foreign applications under the conditions specified in 35 U.S.C. 119(a) through (d) and (f), 172, and 365(a) and (b).

(1)(i) In an original application filed under 35 U.S.C. 111(a), the claim for priority must be presented during the pendency of the application,, and within the later of four months from the actual filing date of the application or sixteen months from the fling date of the prior foreign application. This time period is not extendable. The claim must identify the foreign application for which priority os claimed, as well as any foreign application for the same subject matter and having a filing date before that of the application for which priority is claimed, by specifying the application number, country (or intellectual property authority), day, month, and year of its filing. The time period in this paragraph does not apply to an application for a design patent.

(ii) In an application that entered the national stage from an international application after compliance with 35 U.S.C 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and the Regulations under the PCT."

(2) The claim for priority and the certified copy of the foreign application specified in 35 U.S.C 119(b) or PCT Rule 17 must, in any event, be filed before the patent is granted If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by the processing fee set forth in § 1.17(i), but the patent will not include the priority claim unless corrected by a certificate of correction under 35 U.S C 255 and § 1.323.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [X] such applications have been filed as follows.

NOTE. Where item (c) is entered above and the International Application which designated the U.S. itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, **MONTH**, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
GB	9918912.8	12 AUGUST 1999	[X]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. Section 119(e))

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	**FILING DATE**
_____ / _____	_____
_____ / _____	_____
_____ / _____	_____

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. SECTION 120

[ ] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY*, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

_____

NOTE. If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C Section 120

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179	JULIAN H. COHEN, 20302
JOHN RICHARDS, 31053	WILLIAM R. EVANS 25858
RICHARD J. STREIT, 25765	JANET I. CORD, 33778
PETER D. GALLOWAY, 27885	CLIFFORD J. MASS, 30086
RICHARD P. BERG, 28145	CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

[ ] I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

[ ] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

NOTE. *"Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4) " Section 601.03, M.P.E.P., 7th Ed*

SEND CORRESPONDENCE TO

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

WILLIAM R. EVANS
212-708-1930

(complete the following if applicable)

Since this filing is a [ ] continuation [ ] divisional there is attached hereto a Change of Correspondence Address so that there will be no question as to where the PTO should direct all correspondence.

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

NOTE: Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R Section 1 63(a)(3).

NOTE: Inventors may execute separate declarations/oaths provided <u>each</u> declaration/oath sets forth all the inventors Section 1.63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor 62 Fed. Reg. 53,131, 53,142, October 10, 1997.

Full name of sole or first inventor

1-00

Peter D. Davis
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature (x) X

Date (x) April 16th 2002 **Country of Citizenship** Great Britian

Residence 10 Aston Park, Aston Rowant, Watlington, OX9 5SX, Great Britian GBN

Post Office Address same as above

Full name of second joint inventor, if any

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

Full name of third joint inventor, if any

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[ ] **Signature** for fourth and subsequent joint inventors. *Number of pages added* _____

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. Section 1.47. *Number of pages added* _____

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. Section 1.47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added _____

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[x] This declaration ends with this page.